UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/516,945	08/23/2005	Andrea Capocchi	263361US0PCT	4907

22850 7590 10/20/2008

OBLON, SPIVAK, MCCLELLAND MAIER & NEUSTADT, P.C.
1940 DUKE STREET
ALEXANDRIA, VA 22314

EXAMINER	
HENRY, MICHAEL C	

ART UNIT	PAPER NUMBER
1623	

NOTIFICATION DATE	DELIVERY MODE
10/20/2008	ELECTRONIC

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Notice of the Office communication was sent electronically on above-indicated "Notification Date" to the following e-mail address(es):

patentdocket@oblon.com
oblonpat@oblon.com
jgardner@oblon.com

Office Action Summary	Application No.	Applicant(s)	
	10/516,945	CAPOCCHI, ANDREA	
	Examiner	Art Unit	
	MICHAEL C. HENRY	1623	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *20 May 2008*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *37-48* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *37-48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

A request for continued examination under 37 CFR 1.114, including the fee set forth in 37 CFR 1.17(e), was filed in this application after final rejection. Since this application is eligible for continued examination under 37 CFR 1.114, and the fee set forth in 37 CFR 1.17(e) has been timely paid, the finality of the previous Office action has been withdrawn pursuant to 37 CFR 1.114. Applicant's submission filed on 05/20/08 has been entered.

The following office action is a responsive to the Amendment filed, 05/20/08.

The amendment filed 05/20/08 affects the application, 10/516,945 as follows:

1. Claims 24-36 have been canceled. New Claims 37-48 have been added. Applicant's amendment has overcome the claims objection of the prior office action mailed 11/20/08. Consequently, said claims objection is withdrawn. However, the rejections made under 35 U.S.C. 103(a) are maintained.
2. The responsive to applicants' declaration, amendments and arguments is contained herein below.

Claims 37-48 are pending in application

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 37-48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chiesi et al. (EP 0153998 A2).

In claim 37, applicant claims a process of lyophilization for the preparation of a piroxicam:β-cyclodextrin inclusion compound in a 1:2.5 molar ratio conducted on a kilogram scale comprising: a) dissolving piroxicam and β-cyclodextrin in the molar ratio of 1 to 2.5 and ammonium hydroxide in water brought to a temperature of at least 60 °C;

(b) pouring the piroxicam and β-cyclodextrin dissolved in water from (a) on temperature-controlled shelves of a freeze-dryer pre-cooled to a temperature of at least -30 °C to lower the temperature of the solution to -10 °C at a cooling rate equal to or higher than 1 °C/min, to produce a frozen solution; c) further lowering the temperature of the frozen solution to at least -20 °C; and c) drying the frozen solution under vacuum, wherein the inclusion reaction is complete with complete amorphization of the inclusion compound and complete conversion of the piroxicam to the zwitter-ionic form. Dependent claims 38-40 and 43-45 are drawn to the use of specific temperatures and cooling rates. Claims 41 and 42 are drawn to said method wherein the hot solution is specifically cooled and poured in liquid nitrogen and wherein the product is obtained in specific form. Claim 46 is drawn said method involving the use of specific % concentration and weight ratio of ammonium hydroxide to the piroxicam. Claims 47 and 48 are drawn to said method with specific time of achieving the temperature of freezing the hot solution, and wherein the process is conducted on an industrial scale.

Chiesi et al. disclose a process of lyophilization for the preparation of a piroxicam;β-cyclodextrin inclusion compound in a 1:2.5 molar ratio (0.088:0.220 moles) comprising dissolving piroxicam and β-cyclodextrin in the molar ratio of 1 to 2.5 and 30% ammonium hydroxide in water brought to a temperature of 60 °C; bringing the hot solution to the

temperature of -20 °C of complete freezing and drying the frozen solution under vacuum (freeze drying) (see pages 3-4, example 4). It should also be noted that applicant further claims a lowering of temperature of their solution to a temperature -20 °C which is the same temperature to which Chiesi et al. lowers their solution (see applicant's, claim 37).

The difference between applicant's claimed method and the method of Chiesi et al. is that applicant freezes or cools their solution to a temperature of -10 °C then further to -20 °C whereas Chiesi et al.'s freezes or cools their solution to a temperature of -20 °C, and Chiesi et al.'s is silent about the rate of cooling or freezing rate of said solution. However, Chiesi et al.'s disclose that their solution can be freeze dried in general and thus a skilled artisan would be motivated to adjust the physical parameters used in Chiesi et al.'s method such as temperature so as to optimize the reaction conditions and/or based on factors such as availability or need. Also, even if the rate of cooling or freezing was different, the rate of cooling or freezing should not affect the product formed especially since applicant's claimed lyophilized product is the same as Chiesi et al.'s lyophilized product and since they both used the same reactants to produce their said lyophilized product.

It would have been obvious to one having ordinary skill in the art, at the time the claimed invention was made to have used the process of Chiesi et al., and to make adjustments to condition parameters like the temperature and the rate of cooling or freezing in order to prepare Chiesi et al.'s composition, to treat arthro-rheumatic diseases.

One having ordinary skill in the art would have been motivated, to use the process of Chiesi et al., and to make adjustments to condition parameters like the temperature and the rate of cooling or freezing in order to prepare Chiesi et al.'s composition, to treat arthro-rheumatic

diseases, because a skilled artisan would reasonably be expected to adjust said parameters so as to optimize the reaction conditions and/or based on factors such as availability or need. It should be noted that a skilled artisan would be motivated to adjust the physical parameters used in Chiesi et al.'s method such as temperature, the manner of cooling and rate of cooling the solution so as to optimize the reaction conditions and/or based on factors such as availability or need.

Response to Arguments

Applicant's arguments with respect to claim 37-48 have been considered but are not found convincing.

The Declaration under 37 CFR 1.132 filed 05/20/08 is insufficient to overcome the rejection of claims 37-48 based upon Chiesi et al. (EP 0153998 A2) as set forth in the last Office action because: Applicant's declaration pertains to demonstrating that pre-cooling the shelves of the freeze-dryer to a temperature of -20° C is not sufficient for achieving a cooling rate equal to or higher than 1° C/min, and hence for obtaining a product characterized by: i) completeness of the inclusion reaction; and ii) complete amorphization, and wherein piroxicam is present in the zwitter-ionic form. The declaration fails to set forth any convincing reason or evidence that indicates their claimed process produces a product that is not the same or that is different from the product of the applied prior art document. For example, the declaration discloses that the under the conditions of cooling for Chiesi et al.'s process, "it has been observed that, when the solution reaches the temperature of 50-55°C, β-cyclodextrin begins to re-crystallize causing de-complexation of piroxicam. However, whatever happens to the solution at a temperature of 50-55°C is irrelevant, is not claimed, and does not alter the fact that Chiesi et al.'s process produces a complex of piroxicam:β-cyclodextrin complex of the same molar ratio (1:2.5) of piroxicam to

β-cyclodextrin at the same claimed temperature of -20°C, as claimed by applicant. Furthermore, applicant declaration states that "when the temperature reached a value lower than the eutectic temperature of the product (-18° C), the frozen solution containing crystalline β-cyclodextrin was dried under vacuum. However, a temperature of a value lower than the eutectic temperature of the product (-18°C) includes temperature such as -19°C and even -18.5°C and consequently, applicant has not specifically disclose preparing the frozen solution containing crystalline β-cyclodextrin or the piroxicam:β-cyclodextrin complex at the temperature of -20° C. which is the temperature of Chiesi et al.'s pre-cooled freeze-dryer. In addition, Chiesi et al. disclose the typical endothermic peaks of free piroxicam which appears at about 200°C was absent in their piroxicam:β-cyclodextrin complex (see page 4, line 23 to page 5, line 6). This implies that Chiesi et al.'s piroxicam:β-cyclodextrin complex like applicant's is characterized by complete inclusion. Also, Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex is of the same molar ratio (1:2.5) of piroxicam to β-cyclodextrin which implies that Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex should also be characterized as having complete inclusion and the piroxicam should also be in complete zwitter-ionic form . It should be noted that both applicant's and Chiesi et al.'s lyophilized product is the same piroxicam:β-cyclodextrin complex that are prepared by use of the same reactants. In addition, it should be noted that the applicant in example 1 (on page 10, line 16 to page 11, line 1 of the specification) disclose that "a solution was poured through the tap on the temperature-controlled shelves of the freeze-dryer pre-cooled at -40°C. After 210 min, the frozen product reaches the temperature of -30°C." For, this process the cooling rate is les than that disclosed by applicant in the applicant's declaration presented to demonstrate Chiesi et al.'s cooling rate for the preparation of said complex. However,

applicant's piroxicam:β-cyclodextrin complex at the lower cooling rate still produces amorphous products (see page 11, line 1 of the specification). Thus, Chiesi et al.'s higher cooling rate should also produce an amorphous product. Thus, it should be noted that applicant has not presented any convincing scientific (such as chemical and physical) data that demonstrates Chiesi et al.'s final product (i.e., the piroxicam:β-cyclodextrin complex) is different from applicant's claimed product. Moreover, applicant's has not demonstrated that their method produces a different product from Chiesi et al.'s product.

The declaration and applicant argues that the obtained product was analyzed by differential scanning calorimetry (DSC) analysis. The thermal trace showed an endothermal melting peak at 190-200°C typical of crystalline "uncomplexed" piroxicam. A rough estimation of the area of the peak indicates the presence of at least 20-30% of crystalline piroxicam, confirming that the yield of the process is lower compared to the process claimed in the above-identified application, which specifies completeness of the inclusion reaction. However, Chiesi et al. disclose the typical endothermic peaks of free piroxicam which appears at about 200°C was absent in their piroxicam:β-cyclodextrin complex (see page 4, line 23 to page 5, line 6). This implies that Chiesi et al.'s piroxicam:β-cyclodextrin complex like applicant's is characterized by complete inclusion. Also, Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex is of the same molar ratio (1:2.5) of piroxicam to β-cyclodextrin which implies that Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex should also be characterized as having complete inclusion and the piroxicam should also be in complete zwitter-ionic form . It should be noted that both applicant's and Chiesi et al.'s lyophilized product is the same piroxicam:β-cyclodextrin complex that are prepared by use of the same reactants. In addition, it should be noted that the

applicant in example 1 (on page 10, line 16 to page 11, line 1 of the specification) disclose that "a solution was poured through the tap on the temperature-controlled shelves of the freeze-dryer pre-cooled at -40°C. After 210 min, the frozen product reaches the temperature of -30°C." For, this process the cooling rate is les than that disclosed by applicant in the applicant's declaration presented to demonstrate Chiesi et al.'s cooling rate for the preparation of said complex. However, applicant's piroxicam:β-cyclodextrin complex at the lower cooling rate still produces amorphous products (see page 11, line 1 of the specification). Thus, Chiesi et al.'s higher cooling rate should also produce an amorphous product. Thus, it should be noted that applicant has not presented any convincing scientific (such as chemical and physical) data that demonstrates Chiesi et al.'s final product (i.e., the piroxicam:β-cyclodextrin complex) is different from applicant's claimed product. Moreover, applicant's has not demonstrated that their method produces a different product from Chiesi et al.'s product.

The declaration and applicant argues that pre-cooling the shelves of the freeze-dryer to a temperature of-20° C is not sufficient for achieving a cooling rate equal to or higher than 1° C/min, and hence for obtaining a product characterized by: i) completeness of the inclusion reaction; and ii) complete amorphization, and wherein piroxicam is present in the zwitter-ionic form, as claimed in the above-identified application. However, Chiesi et al. disclose that the typical endothermic peaks of free piroxicam which appears at about 200°C was absent in their piroxicam:β-cyclodextrin complex (see page 4, line 23 to page 5, line 6). This implies that Chiesi et al.'s piroxicam:β-cyclodextrin complex like applicant's is characterized by complete inclusion. Also, Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex is of the same molar ratio (1:2.5) of piroxicam to β-cyclodextrin which implies that Chiesi et al.'s piroxicam:β-

cyclodextrin inclusion complex should also be characterized as having complete inclusion and the piroxicam should also be in complete zwitter-ionic form . It should be noted that both applicant's and Chiesi et al.'s lyophilized product is the same piroxicam:β-cyclodextrin complex that are prepared by use of the same reactants. In addition, it should be noted that the applicant in example 1 (on page 10, line 16 to page 11, line 1 of the specification) disclose that "a solution was poured through the tap on the temperature-controlled shelves of the freeze-dryer pre-cooled at -40°C. After 210 min, the frozen product reaches the temperature of -30°C." For, this process the cooling rate is les than that disclosed by applicant in the applicant's declaration presented to demonstrate Chiesi et al.'s cooling rate for the preparation of said complex. However, applicant's piroxicam:β-cyclodextrin complex at the lower cooling rate still produces amorphous products (see page 11, line 1 of the specification). Thus, Chiesi et al.'s higher cooling rate should also produce an amorphous product. Thus, it should be noted that applicant has not presented any convincing scientific (such as chemical and physical) data that demonstrates Chiesi et al.'s final product (i.e., the piroxicam:β-cyclodextrin complex) is different from applicant's claimed product. Moreover, applicant's has not demonstrated that their method produces a different product from Chiesi et al.'s product.

The declaration discloses that by applying said temperature to the shelves, the solution reaches the freezing temperature of -10°C in 120 min, and hence at a cooling rate of about 0.7°C/min, so lower than 1 °C/min. However, the declaration does not disclose whether or not Chiesi et al.'s product is the same as applicant's at -10°C, especially in terms of being a "frozen solution". Also, one of ordinary skill in the art would expect that by applying a temperature of -20°C to the shelves that Chiesi et al.'s product or process would reach a temperature of -20°C

due to temperature equilibration of the reaction, lyophilization process or system. In fact, based on their teaching one of ordinary skill in the art would deduce that Chiesi et al. applied a temperature of -20°C to the shelves so until the process reached or equilibrated to and occurred to completion at said temperature of -20°C (which is a temperature below the eutectic temperature of -18 °C wherein lyophilization occurs).

The applicant argues that when working on an kilogram scale, the cooling of the aqueous solution to the temperature of complete freezing, i.e., -10 °C, should be carried out very rapidly as claimed, i.e., at cooling rate equal to or higher than 1 °C/min. Only this well-defined and controlled cooling rate allows one to obtain a piroxicam:/β-cyclodextrin complex characterized by complete inclusion and complete amorphization, where the piroxicam is present in the zwitterionic form. However, Chiesi et al. disclose that the typical endothermic peaks of free piroxicam which appears at about 200°C was absent in their piroxicam:β-cyclodextrin complex (see page 4, line 23 to page 5, line 6). This implies that Chiesi et al.'s piroxicam:β-cyclodextrin complex like applicant's is characterized by complete inclusion. Also, Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex is of the same molar ratio (1:2.5) of piroxicam to β-cyclodextrin which implies that Chiesi et al.'s piroxicam:β-cyclodextrin inclusion complex should also be characterized as having complete inclusion and the piroxicam should also be in complete zwitter-ionic form . It should be noted that both applicant's and Chiesi et al.'s lyophilized product is the same piroxicam:β-cyclodextrin complex that are prepared by use of the same reactants. In addition, it should be noted that the applicant in example 1 (on page 10, line 16 to page 11, line 1 of the specification) disclose that "a solution was poured through the tap on the temperature-controlled shelves of the freeze-dryer pre-cooled at -40°C. After 210 min, the

frozen product reaches the temperature of -30°C." For, this process the cooling rate is les than that disclosed by applicant in the applicant's declaration presented to demonstrate Chiesi et al.'s cooling rate for the preparation of said complex. However, applicant's piroxicam:β-cyclodextrin complex at the lower cooling rate still produces amorphous products (see page 11, line 1 of the specification). Thus, Chiesi et al.'s higher cooling rate should also produce an amorphous product. Thus, it should be noted that applicant has not presented any convincing scientific (such as chemical and physical) data that demonstrates Chiesi et al.'s final product (i.e., the piroxicam:β-cyclodextrin complex) is different from applicant's claimed product. Moreover, applicant's has not demonstrated that their method produces a different product from Chiesi et al.'s product.

Conclusion

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Michael C. Henry whose telephone number is 571-272-0652. The examiner can normally be reached on 8.30am-5pm; Mon-Fri. If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Shaojia A. Jiang can be reached on 571-272-0627. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Michael C. Henry
October 11, 2007.

/Shaojia Anna Jiang, Ph.D./
Supervisory Patent Examiner
Art Unit 1623